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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	17

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application N .	Applicant(s)	
	09/421,778	FULLER, JAMES T.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sh t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *9,10,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-17 and 20-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed 10/10/02 in Paper No. 16 has been entered.

Claims 1-27 are pending in the present application.

Claims 9-10 and 18-19 withdrawn from further consideration because they are drawn to non-elected inventions.

Accordingly, claims 1-8, 11-17 and 20-27 are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

Claim Rejections - 35 USC § 102

Claims 24-27 remain rejected under 35 U.S.C. 102(e) as being anticipated by Gu et al. (U.S. Patent No. 6,200,751).

The claims are drawn to a purified, isolated minimal promoter sequence, a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for an antigen of interest, a vector comprising the same nucleic acid construct, preferably a plasmid.

Gu et al. disclosed the isolation and uses of the minimal promoter of the endothelial cell protein C binding protein, EPCR, operably linked to a gene coding for a protein of interest in expression vectors, including plasmid vectors, e.g. pEGFP1 (See col. 4, lines 24-36, lines 45-47; example 3, col. 5, lines 42-49 and the claims). According to Molecular Biotechnology text book (Glick, B.R. & Pasternak, J.J., eds., 1994), a "promoter" is defined as a segment of DNA to which RNA polymerase

attaches. It usually lies upstream of (5' to) a gene. A promoter sequence aligns the RNA polymerase so that transcription will initiate at a specific site (page 475). While "enhancer" is defined as a DNA sequence that increases the transcription of a eukaryotic gene when they are both on the same DNA molecule. Also called enhancer element, enhancer sequence (page 461). As such, the promoter including a region resulting in selective expression in endothelial cells, between –1 and –220 based on the positions relative to the ATG encoding the first amino acid of the murine EPCR protein disclosed by Gu et al. (col. 1, lines 58-63, col. 4, lines 24-36) meets the limitation of the "minimal promoter" of the instant invention which merely requires a promoter sequence without its endogenous enhancer. The encoded green fluorescent protein in the pEGFP1 is an antigen because it is capable of inducing a host immune response in an individual that normally does not naturally habor said gene product. As defined by the instant specification, an antigen refers to any agent, generally a macromolecule, which can elicit an immunological response in an individual (page 7, lines 7-8). Therefore, Gu et al. anticipate the instant claimed invention.

It is noted that the same teachings are disclosed in WO98/20041 (IDS, AT-1).

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 10/10/02 in Paper No. 16 (pages 10-11) have been fully considered.

Applicants argue that Gu fails to teach a promoter that has all native enhancer sequences excised or removed, and assert that none of the promoters taught by Gu

appears to be a minimal promoter. Applicants' arguments are respectively found to be unpersuasive because Gu clearly refers the promoter sequence (-220 to –1) as a minimal promoter as reflected by this statement "Therapeutic strategies include the use of the minimal promoter (-220 to –1) for expression in all endothelial cells..." (see col. 2, lines 15-17). Applicants have not provided a single factual evidence to support Applicants' assertion that the promoter sequence (-220 to –1) still contains any normal enhancer site.

Therefore, claims 24-27 remain rejected under 35 U.S.C. 102(e) as being anticipated by Gu et al. for the reasons set forth above.

Claims 1, 12 and 24-27 remain rejected under 35 U.S.C. 102(b) as being anticipated by Burns et al. (Blood 81:1558-1566, 1993) or by Deb et al. (J. Virology 66:6164-6170, 1992) for the same reasons set forth in the previous Office Action.

Burns et al. teach the preparation of a pHLA A2-CAT116 plasmid comprising a minimal HLA A2 promoter having CCAAT box and TATA box motifs operably linked to a CAT gene (see Fig. 1 and Materials and Methods). Burns et al. further teach that the pHLA A2-CAT116 plasmid is transfected in Jurkat cells (page 1560, col. 1, section "Transfection"). A bacterial chloramphenicol acetyltransferase (CAT) gene product is an antigen since it is capable of eliciting an immunological response in a host.

Deb et al. disclose a plasmid comprising a minimal human proliferating cell antigen (PCNA) promoter with a TATA box alone operably linked to a CAT gene (see Fig. 6) for transfection in Hela cells. A bacterial chloramphenicol acetyltransferase

(CAT) gene product is an antigen since it is capable of eliciting an immunological response in a host.

Accordingly, Burns et al. and Deb et al. anticipate the instant claims.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 10/10/02 in Paper No. 16 (pages 12-14) have been fully considered.

With respect to the reference of Burns et al., Applicants assert that the authors conclude that the dual CCAAT boxes found in the –116 to –1 promoter sequence serve as native enhancer sequences to the HLA A2 promoter, and therefore the reference fails to anticipate the instant claims. Applicants' argument is found unpersuasive because Examiner could not find where in the reference that Burns et al. refer the dual CCAAT boxes as native enhancer sequences, and Applicants fail to point out the exact page and line numbers where such conclusion is made by the authors. It is well known in the art that the CCAAT box motif in a minimal promoter sequence is not an enhancer element (please check the most basic biochemical text-book).

With respect to the reference of Deb et al., Applicants argue mainly that it is unclear if the various PCNA promoters discussed by Deb were indeed "minimal promoters" where all native enhancer sequences had been removed. Applicants' argument is again not found to be persuasive because Applicants have not provided any factual evidence to show that any of PCNA promoters of Deb et al. still contains endogenous or native enhancer elements, while Deb et al. describe her plasmid

comprising **a minimal human proliferating cell antigen (PCNA) promoter** with a TATA box alone operably linked to a CAT gene (see Fig. 6).

Accordingly, claims 1, 12 and 24-27 remain rejected for the reasons set forth above.

Following is a new ground of rejection.

Claim Rejections - 35 USC § 102

Claims 1-8, 11-12, 15-17, 20, 23 and 25-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Johnston et al. (U.S. Patent No. 6,194,389; IDS, AK-1) as evidenced by Miwa et al. (Mol. Cell. Biol. 7:2803-2813, 1987).

The claims are directed to a method of obtaining expression in mammalian cells of an antigen of interest, which method comprises transferring into said cells a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for the antigen, whereafter said coding sequence is expressed in said mammalian cells, coated particles comprising carrier particles coated with the same nucleic acid construct, a particle accelerating device loaded with the same coated particles and the same nucleic acid construct .

Johnston et al. disclose a method for obtaining a protective immune response in a vertebrate subject by *in situ* microprojectile bombardment by providing microprojectiles carrying a DNA sequence comprising in the 5' to 3' direction a regulatory element functional in the tissue cells and a gene positioned downstream of

the regulatory element and under the transcriptional control thereof, the gene coding for a protective immune response-producing protein or polypeptide, wherein the microprojectiles comprise a material selected from the group consisting of metal (gold, tungsten, iridium), glass, silica, ice , polyethylene, polycarbonate, graphite and diamond; then accelerating the microprojectiles at the subject using a microprojectile acceleration cell transformation apparatus (See abstract, the claims and particularly col. 5 and 6). Johnston et al. teach that the regulatory sequences which may be used to provide transcriptional control of the gene in the polynucleic acid sequence are generally promoters which are operable in the target tissue cells, and that other regulatory elements which may optionally be incorportated into the polynucleic acid sequence include enhancers, termination sequences and others to obtain the desired degree of expression of the gene in a cell (col. 5, lines 42-45 and lines 65-67). The polynucleic acid sequence carried by the microprojectile is a recombinant construct of a gene and a regulatory element, which can be in the form of a plasmid (col. 4, lines 37-51). Exemplary promoters that Johnston et al. specifically teach include the human alpha-actin promoter of Miwa and Kedes (Mol. Cell Biol. 2803, 1987), the human beta-actin promoter, the troponin T gene promoter, the human heat shock protein 70 promoter, the metallothionin gene promoter among others. Additionally, exemplary of genes that code for proteins or peptides which produce an immune response are genes encoding for subunit vaccines against enteroviruses, surface antigen of the hepatitis B (col. 5, lines 4-14). Miwa and Kedes (Mol. Cell Biol. 2803, 1987) teach a promoter region of the human alpha-cardiac actin gene (an upstream region from the transcription initiation site

to –177 base pair) that lacks an enhancer element (see abstract), and therefore the disclosed promoter of Miwa and Kedes is a minimal promoter as defined by Applicants as an "enhancerless promoter sequence" (see specification page 4, lines 7-8). Johnston et al. further teach that the tissue cells to be genetically modified by their method can be cells either in a tissue (*in situ* or *in vivo*) or removed from its tissue of origin (*in vitro or ex vivo*) from an animal that encompasses vertebrates, mammals including human (see line 55 of col. 3 continues to line 36 of col. 4).

Accordingly, the teachings of Johnston et al. meet every limitation of the claims, and therefore Johnston et al. anticipate the instant claimed invention as evidenced by Miwa and Kedes.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 10/10/02 in Paper No. 16 (pages 12-14) have been fully considered.

Applicants argue mainly that Johnston does not describe applicants' minimal promoters, and that the passage discussing optional regulatory elements (including enhancers) does not relate to the portions of the specification that are specific to promoters. There is no evidence of record that Johnston was referring to native enhancers optionally added to specific promoters. With respect to Miwa abstract, Applicants argue that Miwa mentions that certain insertion or deletion mutants were made to the promoters, and that Applicants' recited minimal promoters require that the native enhancer is excised from the promoter, and therefore Miwa's mutant promoters

do not fit the description of a minimal promoter. Applicants' arguments are respectfully found to be unpersuasive for the following reasons.

Firstly, Johnston et al. clearly teach the use of the human alpha-actin promoter disclosed by Miwa and Kedes in the article Mol. Cell Biol. 2803, 1987 as one of the promoters in a polynucleic acid sequence (can be in the form of a plasmid) carried by the microprojectiles, and that Miwa and Kedes (Mol. Cell Biol. 2803, 1987) disclose a promoter region of the human alpha-cardiac actin gene (an upstream region from the transcription initiation site to –177 base pair) that lacks an enhancer element (see abstract), and therefore the promoter of Miwa & Kedes is qualified as a minimal promoter as defined by Applicants as an "enhancerless promoter sequence", regardless whether the promoter contains any mutation or not. Furthermore, Applicants also contemplate functional variant minimal promoter containing insertion, deletion and substitution for a native minimal promoter (see specification, page 10, line 27 continues to line 2 of page 11).

Secondly, when one of ordinary skilled artisan in the art refers to a promoter, it is not necessarily that the promoter must contain its native enhancer. This is because promoter sequence and enhancer sequence are two separate entities having different functions. According to a Molecular Biotechnology text book (Glick, B.R. & Pasternak, J.J., eds., 1994), a "promoter" is defined as a segment of DNA to which RNA polymerase attaches. It usually lies upstream of (5' to) a gene. A promoter sequence aligns the RNA polymerase so that transcription will initiate at a specific site (page 475). While "enhancer" is defined as a DNA sequence that increases the transcription of a

eukaryotic gene when they are both on the same DNA molecule. Also called enhancer element, enhancer sequence (page 461). Therefore, Johnston does refer that other regulatory elements such as enhancers (native or exogenous) termination sequences and polyadenylation sites may optionally be incorporated into the polynucleic acid sequence for obtained the desired degree of expression of a gene in a cell (see line 65 of col. 5 continues to line 3 of col. 6).

Accordingly, claims 1-8, 11-12, 15-17, 20, 23 and 25-27 are rejected for the reasons set forth above. ***Examiner notes that the above rejection is a new ground of rejection for claims 5-6.***

Claims 1, 5, 7, 12-14 and 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Hofmann et al. (Proc. Natl. Acad. Sci. 93:5185-5190, 1996).

The claims are drawn to a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence, a vector comprising the same nucleic acid construct, and a method of obtaining expression in mammalian cells of an antigen of interest using the same. Claims 13 and 14 are drawn to the same method wherein the minimal promoter sequence consists essentially of a hCMV immediate early promoter sequence, a pseudorabies virus early promoter sequence, a simian cytomegalovirus immediate early promoter sequence or a functional variant thereof, and wherein the minimal promoter sequence consists essentially of the sequence spanning positions 0 to –118 of the hCMV immediate early promoter region or a functional variant of the said spanning sequence, respectively. It is noted that the scope of claim 1 and its

dependent claims encompasses both *in vitro* and *in vivo* methods of obtaining expression in mammalian cells of an antigen of interest.

With respect to an *in vitro* method, Hofmann et al. disclosed a recombinant retroviral vector construct (SIN-RetroTet vector) containing an autoregulatory cassette comprising a heptamerized tet operator sequence $(TetO)_7$ fused to the human CMV immediate early minimal promoter $P_{hCMV*-1}$ (See Fig. 1). Analysis of transduced C57BL/6 primary myoblasts (cells taken from a mouse) revealed that the construct yields low basal levels of gene expression and induction of one to two orders of magnitude. In this instant, beta-galactosidase is the polypeptide of interest. The human CMV immediate early minimal promoter $P_{hCMV*-1}$ falls within the scope of a functional variant, the disclosure of Hofmann et al fulfilled the required elements in the claims. With respect to the limitation recited in claims 14 and 22, "consisting essentially of the sequence spanning positions 0 to 118 of the hCMV.....or a functional variant of the said spanning sequence", the claim reads over the $P_{hCMV*-1}$ promoter disclosed by Hofmann et al. for which the instant specification has no written support for. Thus, the reference anticipates the instant claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 10/10/02 in Paper No. 16 (pages 8-10) have been fully considered.

Applicants argue that the term "minimal promoter" is clearly and unambiguously defined in the specification as only encompassing those promoters where the native

enhancer has been excised or otherwise removed, and imply that the $P_{hCMV*-1}$ promoter of Hofmann does not have all native enhancer sequences excised or removed. Applicants further argue that the Examiner provides no supporting evidence to back up the argument that the $P_{hCMV*-1}$ promoter of Hofmann is a functional variant of a minimal promoter. For these reasons, Hofmann does not anticipate the instant claims. Applicants' arguments are found unpersuasive for the reasons discussed below.

Hofmann clearly teaches that the $P_{hCMV*-1}$ promoter contains a human CMV immediate early **minimal promoter** that has a weak promoter activity, indicating that the human CMV immediate early minimal promoter does not contain its native enhancer. Applicants have not provided any factual evidence to support Applicants' doubt that the $P_{hCMV*-1}$ promoter of Hofmann contains endogenous or native enhancer sequences. To further support Examiner's position that the CMV immediate early minimal promoter of Hofmann does not have the native enhancer, Gossen et al. (Proc. Natl. Acad. Sci. 89:5547-5551, 1992) teach that the minimal promoter, P_{hCMV*} has its enhancer region of P_{hCMV} being removed (see page 5548, col. 1, first full paragraph), and the same minimal promoter P_{hCMV*} construct of Gossen et al. was obtained by Hofmann to construct the $P_{hCMV*-1}$ promoter (see Hofmann, page 5186, col. 1, under Vector construction section). As defined by the present application a "minimal promoter" is a promoter sequence is used in its enhancerless form (i.e., it is not coupled with its native enhancer sequence when used in the context of the present invention, however, it may be used in a construct which contains other heterologous enhancer sequences) (see specification, page 10, lines 7-16). Additionally, as defined by the

present application a "functional variant sequence" may vary from a native promoter sequence by one or more base substitutions, deletions or insertions. There may be from 1 to 30, for example from 5 to 20, base substitutions and/or from 1 to 30, for example from 5 to 20, base deletions and/or from 1 to 30, for example 5 to 20, base insertions (see specification, line 27 on page 10 continues to line 2 of page 11). Therefore, based on the broad definitions for "minimal promoter and "functional variant promoter" of the present application, the teachings of Hofmann meet all the limitations of the instant claims.

Accordingly, claims 1, 5, 7, 12-14 and 25-27 are rejected for the reasons set forth above. ***Examiner notes that the above rejection is a new ground of rejection for claim 5.***

Claim Rejections - 35 USC § 103

Claims 15 and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston et al. (U.S. Patent No. 6,194,389; IDS, AK-1) with evidence by Miwa et al. (Mol. Cell. Biol. 7:2803-2813, 1987) and in view of Hofmann et al. (Proc. Natl. Acad. Sci. 93:5185-5190, 1996).

The claims are drawn to coated particles suitable for use in particle-mediated nucleic acid immunization, which paticles comprise carrier particles coated with a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence encoding an antigen; the same wherein the minimal promoter sequence consists essentially of a human cytomegalovirus (hCMV) immediate early

promoter sequence, a psuedorabies virus (PRV) early promoter region, a simian cytomegalovirus (sCMV) immediate early promoter sequence or a functional variant thereof, and preferably the same wherein the minimal promoter squence consists essentially of the sequence spanning positions 0 to –118 of the hCMV immediate early promoter region or a functional variant of the said spanning sequence.

Johnston et al. disclose a method for obtaining a protective immune response in a vertebrate subject by *in situ* microprojectile bombardment by providing microprojectiles carrying a DNA sequence comprising in the 5' to 3' direction a regulatory element functional in the tissue cells and a gene positioned downstream of the regulatory element and under the transcriptional control thereof, the gene coding for a protective immune response-producing protein or polypeptide, wherein the microprojectiles comprise a material selected from the group consisting of metal (gold, tungsten, iridium), glass, silica, ice , polyethylene, polycarbonate, graphite and diamond; then accelerating the microprojectiles at the subject using a microprojectile acceleration cell transformation apparatus (See abstract, the claims and particularly col. 5 and 6). Johnston et al. teach that the regulatory sequences which may be used to provide transcriptional control of the gene in the polynucleic acid sequence are generally promoters which are operable in the target tissue cells, and that other regulatory elements which may optionally be incorportated into the polynucleic acid sequence include enhancers, termination sequences and others to obtain the desired degree of expression of the gene in a cell (col. 5, lines 42-45 and lines 65-67). The polynucleic acid sequence carried by the microprojectile is a recombinant construct of a gene and a

regulatory element, which can be in the form of a plasmid (col. 4, lines 37-51). Exemplary promoters that Johnston et al. specifically teach include the human alpha-actin promoter of Miwa and Kedes (Mol. Cell Biol. 2803, 1987), the human beta-actin promoter, the troponin T gene promoter, the human heat shock protein 70 promoter, the metallothionin gene promoter among others. Additionally, exemplary of genes that code for proteins or peptides which produce an immune response are genes encoding for subunit vaccines against enteroviruses, surface antigen of the hepatitis B (col. 5, lines 4-14). Miwa and Kedes (Mol. Cell Biol. 2803, 1987) teach a promoter region of the human alpha-cardiac actin gene (an upstream region from the transcription initiation site to –177 base pair) that lacks an enhancer element (see abstract), and therefore the disclosed promoter of Miwa and Kedes is a minimal promoter as defined by Applicants as an "enhancerless promoter sequence" (see specification page 4, lines 7-8). Johnston et al. further teach that the tissue cells to be genetically modified by their method can be cells either in a tissue (*in situ* or *in vivo*) or removed from its tissue of origin (*in vitro* or *ex vivo*) from an animal that encompasses vertebrates, mammals including human (see line 55 of col. 3 continues to line 36 of col. 4).

Johnston et al. do not specifically teach the make and use of carrier particles coated with a nucleic acid construct comprising the selected minimal promoter sequence as recited in claims 21 or 22.

However, at the effective filing date of the present application, Hofmann et al. already disclosed a recombinant retroviral vector construct (SIN-RetroTet vector) containing an autoregulatory cassette comprising a heptamerized tet operator sequence

$(TetO)_7$ fused to the human CMV immediate early minimal promoter $P_{hCMV*-1}$ (See Fig. 1) for induction of transgene expression in response to tetracycline. Hofmann et al. further teach that the recombinant retroviral vector construct allows rapid delivery of inducible genes and should have broad applications to cultured cells, transgenic animals and gene therapy (see abstract and discussion). As defined by the present application a "minimal promoter" is a promoter sequence is used in its enhancerless form (i.e., it is not coupled with its native enhancer sequence when used in the context of the present invention, however, it may be used in a construct which contains other heterologous enhancer sequences) (see specification, page 10, lines 7-16). Additionally, as defined by the present application a "functional variant sequence" may vary from a native promoter sequence by one or more base substitutions, deletions or insertions. There may be from 1 to 30, for example from 5 to 20, base substitutions and/or from 1 to 30, for example from 5 to 20, base deletions and/or from 1 to 30, for example 5 to 20, base insertions (see specification, line 27 on page 10 continues to line 2 of page 11). Therefore, based on the broad definitions for "minimal promoter and "functional variant promoter" of the present application, the human CMV immediate early minimal promoter $P_{hCMV*-1}$ taught by Hofmann falls within the scope of a functional variant minimal promoter of the instant claims.

Accordingly, it would have been obvious and within the scope of skill for an ordinary skilled artisan at the filing date of the present application to modify the method and composition taught by Johnston et al. by utilizing the recombinant retroviral

construct of Hofmann for delivering a desired transgene to a subject for producing a protective immune response.

One of ordinary skilled artisan would have been motivated to carry out the above modification because the recombinant retroviral construct of Hofmann et al. would allow one of ordinary skilled artisan to regulate the desired levels of transgene in cells *in vivo* under the control of tetracycline for the purpose of obtaining the desired immune responses in a vertebrate. Additionally, as taught by Hofmann that the recombinant retroviral construct also allows rapid delivery of inducible genes in cells and that it has broad applications including gene therapy (see abstract and discussion).

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to LIE, Tiffany Tabb, whose telephone number is (703) 605-1238.

Quang Nguyen, Ph.D.

JAMES KETTER
PRIMARY EXAMINER